New Applications of Flow Chemistry in Industry and Academia

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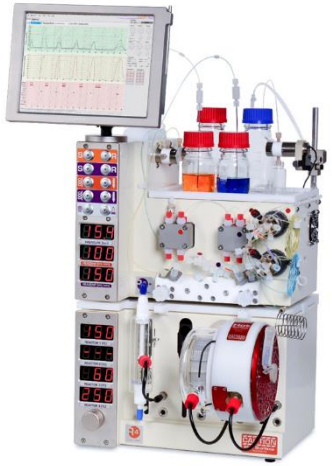
Vapourtec Key Facts

- Established 2003
- First Flow Chemistry System sold – May 2006
- Installed 370 systems worldwide
- Vapourtec only produce flow chemistry systems
- 250 peer-review publications using our systems to date

Vapourtec Systems

- Vapourtec manufacture laboratory scale flow chemistry systems
  - R-Series (launched 2006); a highly specified modular system capable of either standalone operation or integration with other equipment to provide a versatile automated flow chemistry
  - E-Series (launched 2012); an easy to use entry level system platform ideal for new users and University teaching

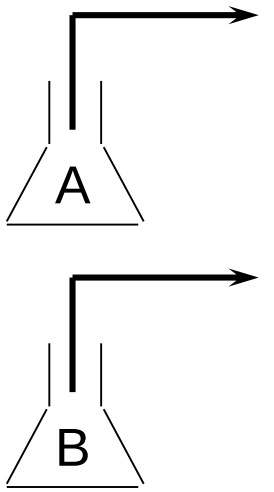


Where does Vapourtec fit in ?

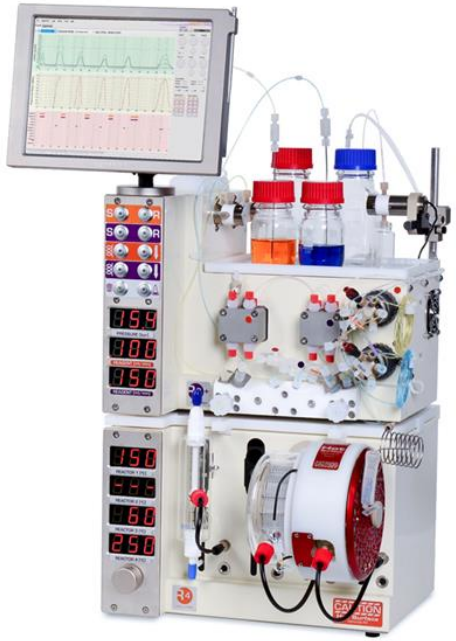
Flow principles can be applied to >14 orders of magnitude in scale, from earliest chemistry to late manufacturing

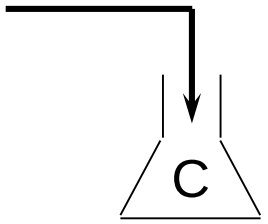
nano	micro	meso	kilo lab	pilot plant	manufacturing

ng → *μg* → *mg* → *g* → *kg* → *10 kg* → *100 kg* → *multi-ton*



Vapourtec R4





50 mg (convenience)
to 4000 g / day (“real chemistry”)

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The Vapourtec R-Series (launched 2006)

- Highly specified modular system
- Capable of integrating with other equipment
- Pump options up to 200 bar
- Same reactor range as E-Series
- Either 2, 3 or 4 independent pumps
- 4 independently set reactors
- 270 systems installed worldwide
- Features in >200 peer reviewed publications

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The Vapourtec E-Series (launched Dec 2012)

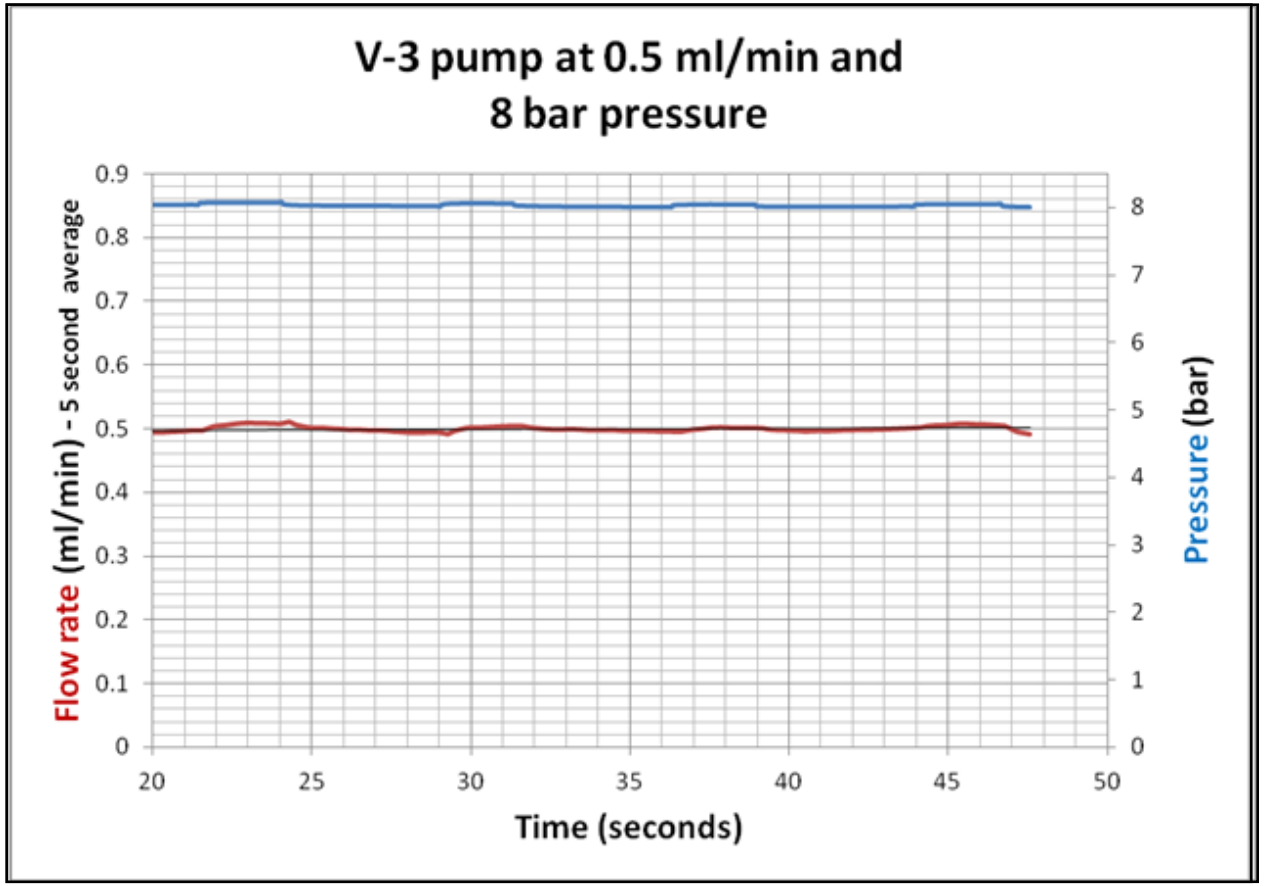
- Entry-level system
- Ideal for academic groups
- Stand alone operation only
- V-3 pumps up to 10 bar pressure
- Same reactor range as R-Series
- Either 2 or 3 independent pumps
- 2 independent reactor positions
- Does not interface with other equipment
- 110 systems installed to date

Vapourtec E-Series – The V-3 pump

- Pressure
  - 10 bar
- Compatibility
  - Strong acids and bases
  - Organometallics
  - Suspensions/slurries
  - Gases
- Smooth

Vapourtec V-3 Pump – Advanced control

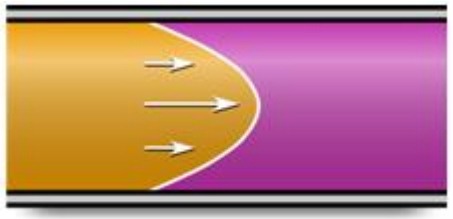
After



Pressure and flow rate of peristaltic V-3 pump showing the benefit of Vapourtec Adaptive Pump Rotor Control

Applications in Continuous Flow

Biphasic Reactions in Continuous Flow



Laminar flow or streamline flow in pipes (or tubes) occurs when a fluid flows in parallel layers, with no disruption between the layers. At low velocities, the fluid flows without lateral mixing, adjacent layers slide past one another like playing cards.

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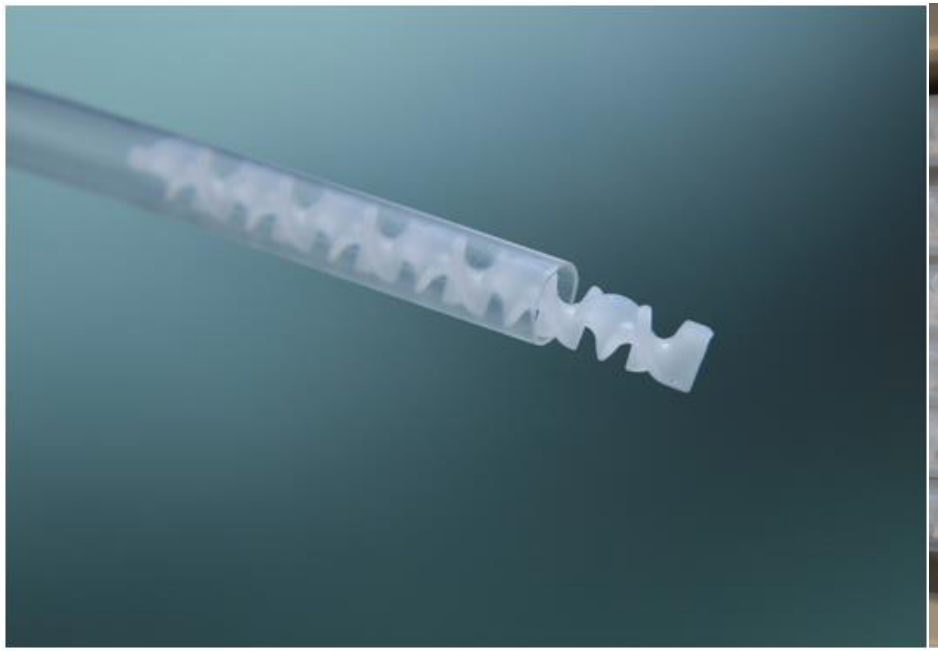
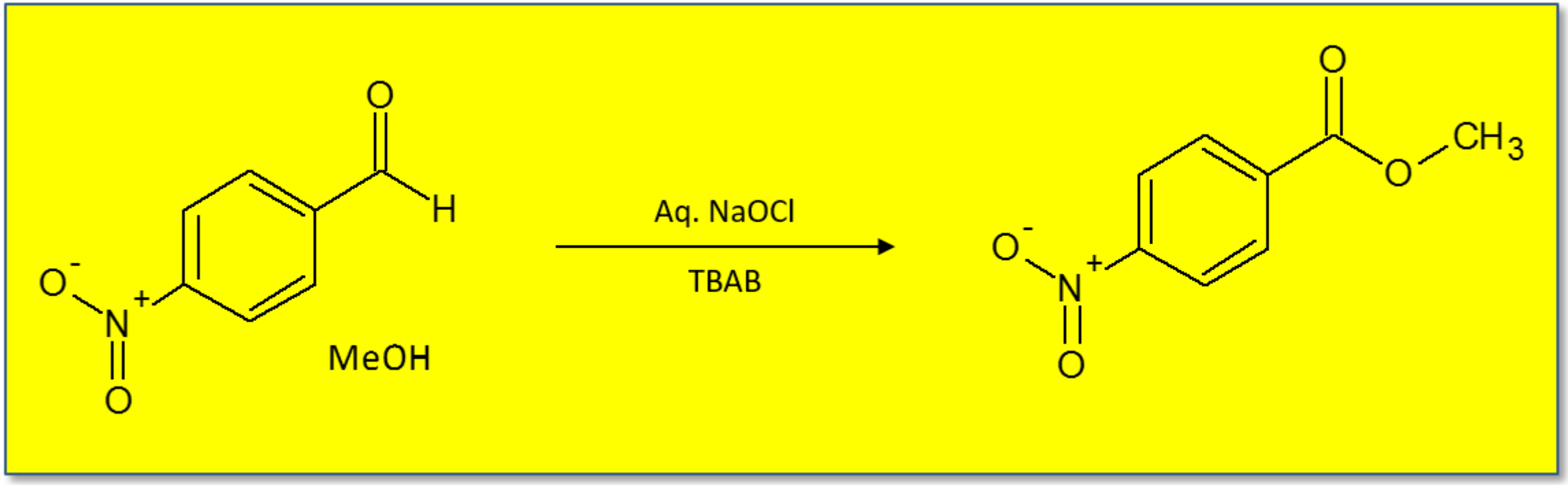
Biphasic Reactions in Continuous Flow



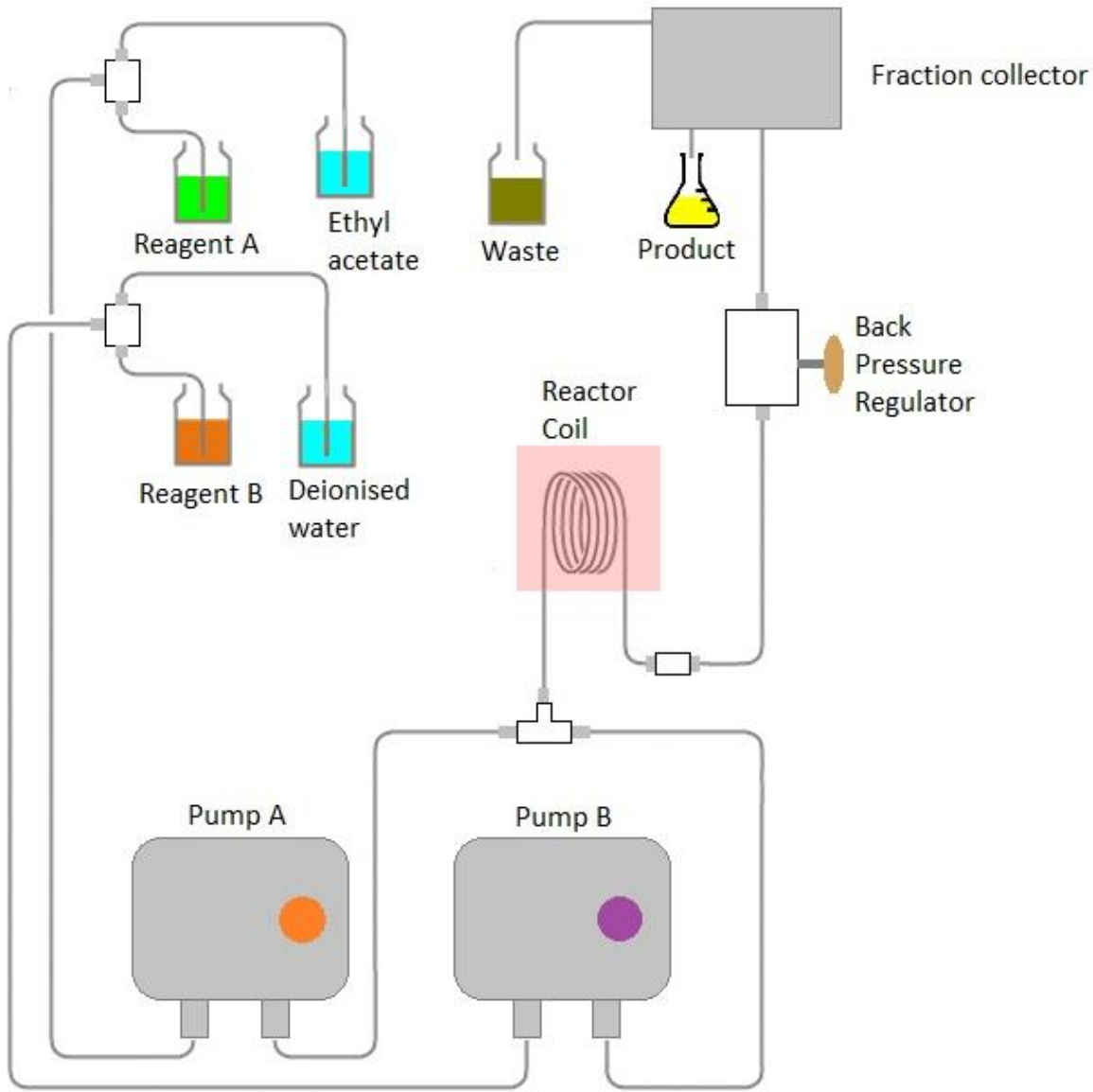
Static mixing inserts

Static Mixer Reactor

Biphasic Steven's Oxidation



One example of a reaction with a challenging mixing behaviour is an ester synthesis via a Steven's oxidation, which uses aqueous sodium hypochlorite to oxidise an aldehyde to an ester in the presence of an alcohol, allowing the direct synthesis of the ester from the aldehyde.

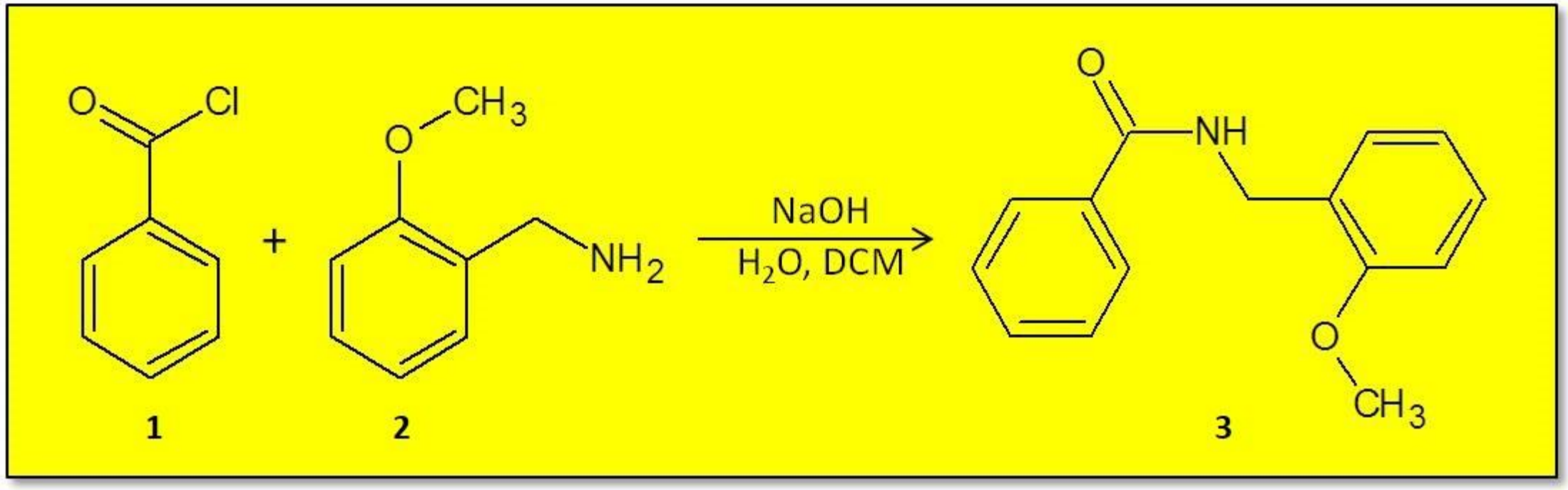

Fraction collector
Reagent A
Ethyl acetate
Waste
Product
Back Pressure Regulator
Reactor Coil
Reagent B
Deionised water
Pump A
Pump B

Biphasic Steven's Oxidation

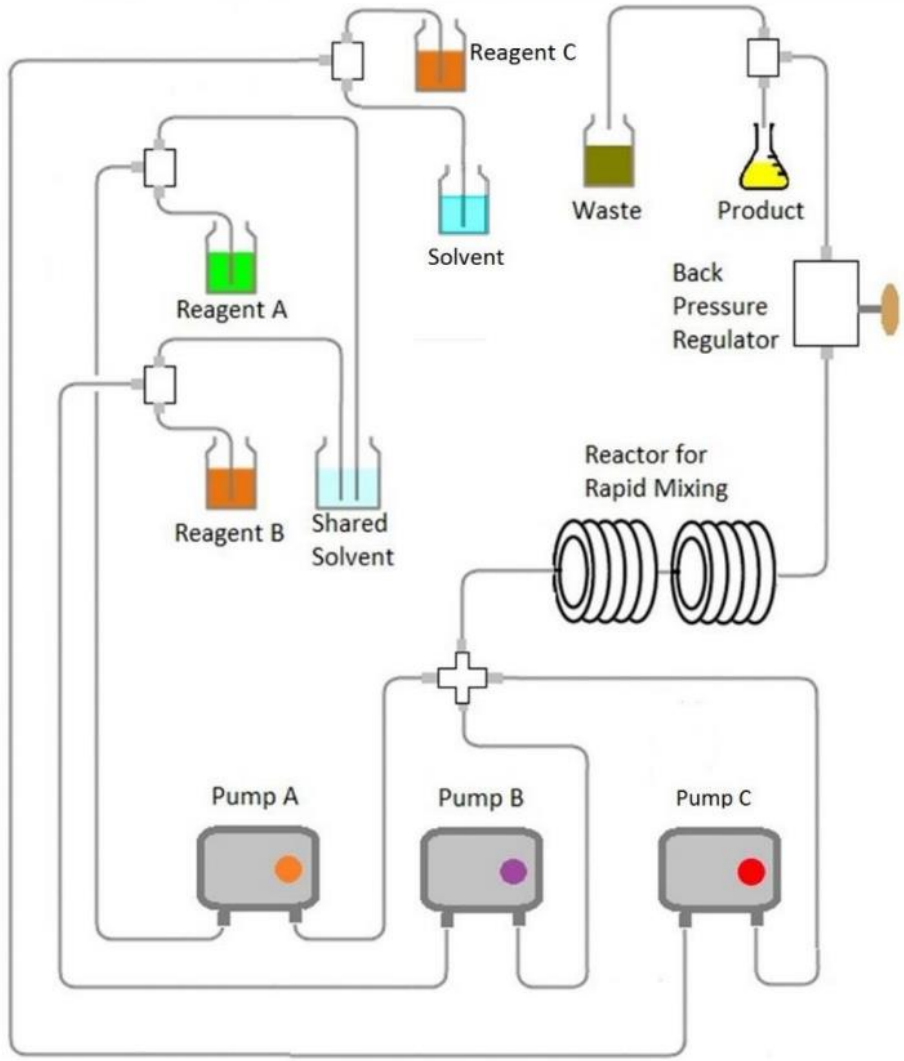
- Vapourtec Reactors for Rapid Mixing and **High Flow rate** pump module
- Greater than **99.9%** conversion at a **58 s** residence time in a **60 ml** reactor
- Over **4.5 kg/day** production with just the footprint of a Vapourtec R-Series

Reactor	Residence Time (s)	Conversion (%)	Throughput (gh^{-1})
10 ml Standard	58	64.6	22.4
20 ml Mixed	58	94.5	67.8
60 ml Mixed	58	99.9	203.3

Biphasic Amide Formation



A method developed to permit amide formation without the need for 2 equivalents of amine – biphasic separation prevents reaction of base with the acid chloride


Reagent C
Waste
Product
Solvent
Reagent A
Back
Pressure
Regulator
Reagent B
Shared
Solvent
Reactor for
Rapid Mixing
Pump A
Pump B
Pump C

Biphasic Amide Formation

- Greater than **95%** yield from a biphasic reaction
- **14.5 g/h** at 50 °C
- Useful synthetic strategy accelerated using intense mixing

Vapourtec wish to thank Dr Claudio Battilocchio and Prof. Steven Ley at the University of Cambridge for conducting the experimental work and providing additional information for this application note.

Solids in Flow?!

- Common concern about blocking the flow path
- Difficult to achieve pressure – blocking pressure regulators

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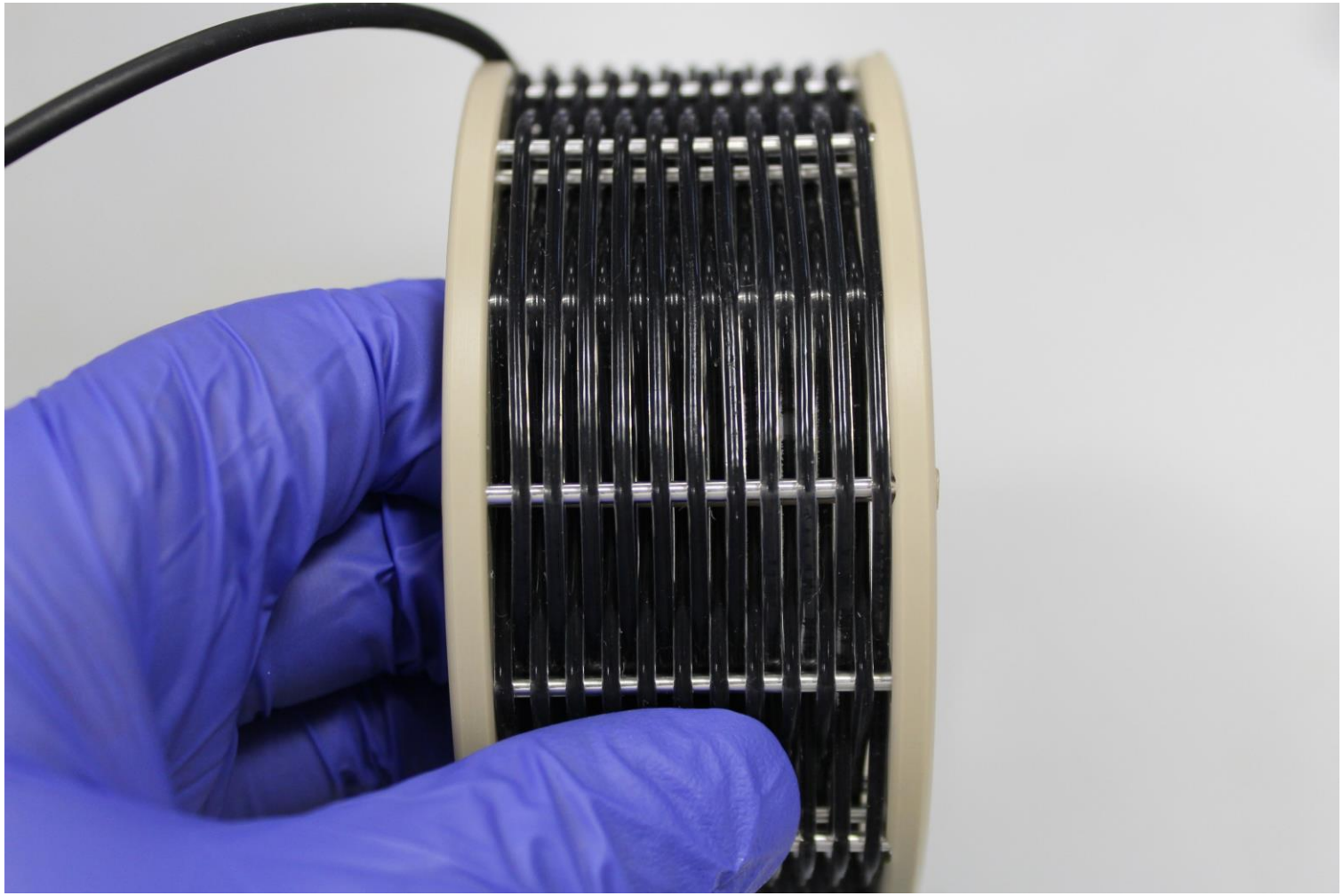
	TEMPERATURE (°C)															
	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250
1 Butanol	0.5	0.8	1.1	1.5	2.1	2.8	3.7	4.7	6.1	7.7	9.5	11.7	14.2	17.1	20.4	24.1
1 Propanol	1.2	1.6	2.3	3.2	4.1	5.4	7.0	9.0	11.3	14.0	17.2	20.9	25.2	30.0	35.5	41.7
Acetic Acid	0.6	0.8	1.1	1.4	1.9	2.5	3.2	4.1	5.1	6.3	7.8	9.5	11.4	13.7	16.3	19.2
Acetone	3.7	4.8	6.1	7.6	9.5	11.6	14.1	16.9	20.1	23.8	27.9	32.5	37.6	43.2	49.4	56.2
Acetonitrile	2.0	2.7	3.7	4.8	6.3	8.1	10.3	13.0	16.3	20.2	24.8	30.2	36.6	44.0	52.5	62.3
Benzene	1.8	2.5	3.1	3.9	4.9	5.9	7.2	8.6	10.3	12.2	14.4	16.9	19.6	22.7	26.1	29.9
Carbon tetrachloride	1.9	2.5	3.2	4.0	5.0	6.1	7.4	8.9	10.5	12.4	14.6	16.9	19.6	22.4	25.6	29.0
Chloroform	3.1	4.0	5.0	6.3	7.8	9.6	11.7	14.1	16.8	19.9	23.4	27.3	31.7	36.6	42.0	47.9
Cyclohexane	1.7	2.2	2.9	3.6	4.5	5.5	6.7	8.1	9.7	11.5	13.5	15.7	18.3	21.0	24.1	27.5
DCM	5.9	7.5	9.4	11.7	14.3	17.4	20.9	24.9	29.4	34.5	40.2	46.5	53.5	61.2	69.6	78.7
Di ethyl ether	6.1	7.6	9.4	11.5	14.0	16.8	20.0	23.6	27.7	32.2	37.3	42.9	49.0	55.7	63.1	71.0
Diglyme	0.1	0.2	0.3	0.4	0.6	0.8	1.0	1.3	1.7	2.2	2.8	3.6	4.4	5.5	6.7	8.1
Dioxane	1.0	1.3	1.7	2.3	2.9	3.7	4.7	5.9	7.2	8.8	10.6	12.7	15.2	17.9	21.0	24.4
DME	1.2	1.6	2.0	2.5	3.0	3.7	4.5	5.4	6.4	7.5	8.8	10.2	11.8	13.5	15.4	17.5
DMF	0.2	0.3	0.4	0.6	0.8	1.0	1.3	1.7	2.1	2.6	3.2	3.9	4.7	5.6	6.6	7.8
DMSO	0.1	0.1	0.1	0.2	0.2	0.3	0.4	0.7	0.9	1.2	1.5	2.0	2.5	3.2	4.0	5.0
Ethanol	2.1	2.9	4.0	5.3	7.0	9.1	11.6	14.7	18.3	22.6	27.6	33.4	40.1	47.7	56.3	65.9
Ether	6.1	7.6	9.4	11.5	14.0	16.8	20.0	23.6	27.7	32.2	37.3	42.9	49.0	55.7	63.1	71.0
Ethyl Acetate	2.0	2.7	3.5	4.4	5.6	6.9	8.5	10.4	12.5	14.9	17.6	20.7	24.1	27.9	32.1	36.8
Formic Acid	1.0	1.3	1.7	2.2	2.9	3.6	4.5	5.6	6.9	8.3	10.0	11.9	14.1	16.6	19.4	22.5
Heptane	1.2	1.7	2.2	2.9	3.8	4.8	6.1	7.6	9.5	11.6	14.1	16.9	20.2	24.0	28.2	33.0
Hexane	2.5	3.1	4.0	5.0	6.1	7.4	9.0	10.7	12.7	14.9	17.4	20.2	23.2	26.5	30.1	34.1
IPA	2.0	2.8	3.8	5.1	6.7	8.7	11.0	13.9	17.2	21.2	25.7	30.9	36.8	43.5	51.0	59.4
MEK	1.9	2.4	3.1	4.0	4.9	6.1	7.5	9.0	10.8	12.8	15.1	17.6	20.4	23.4	26.8	30.5
MeOH	3.3	4.5	6.0	7.9	10.2	13.0	16.5	20.6	25.4	31.1	37.7	45.3	54.0	63.9	75.1	87.7
NMP	0.0	0.0	0.1	0.1	0.1	0.2	0.3	0.4	0.5	0.7	1.0	1.2	1.6	2.0	2.5	3.1
Pentane	5.9	7.3	9.0	10.9	13.0	15.5	18.3	21.4	24.8	28.5	32.7	37.2	42.0	47.3	52.9	59.0
p-Xylene	0.3	0.4	0.6	0.8	1.1	1.4	1.7	2.2	2.7	3.4	4.1	5.0	6.0	7.1	8.4	9.9
t Butyl Alcohol	1.9	2.7	3.6	4.8	6.3	8.1	10.2	12.7	15.6	19.0	22.9	27.3	32.3	37.8	44.0	50.8
THF	2.7	3.5	4.4	5.5	6.9	8.4	10.1	12.2	14.4	17.0	19.9	23.1	26.6	30.5	34.7	39.4
Toluene	0.7	1.0	1.3	1.7	2.2	2.7	3.4	4.2	5.1	6.2	7.5	8.9	10.5	12.3	14.4	16.7
Water	1.0	1.2	1.8	2.6	3.7	5.0	6.6	8.5	10.8	13.5	16.5	20.0	23.8	28.1	32.8	37.9

Solids in Flow?!

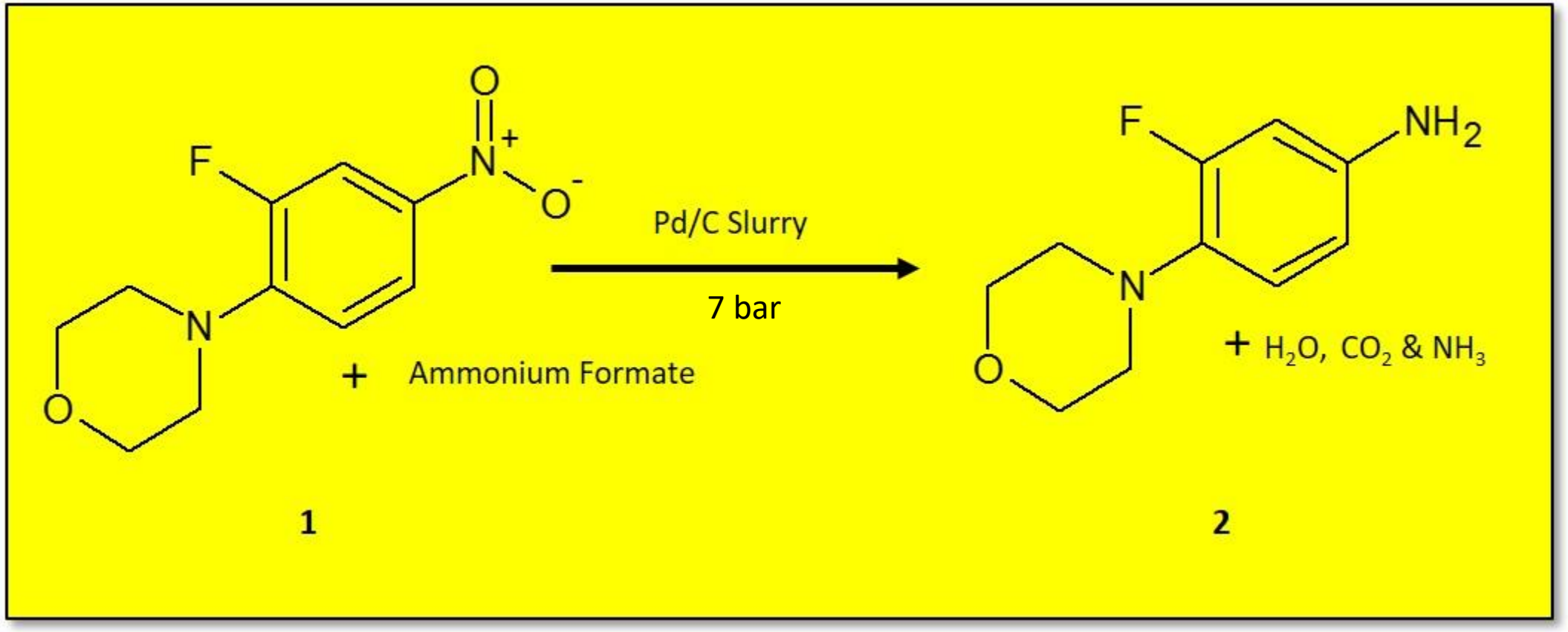
- Common concern about blocking the flow path
- Difficult to achieve pressure – blocking pressure regulators

- Vapourtec have been using solids in slurries at pressure using V-3 pumps

Palladium on Charcoal Slurries

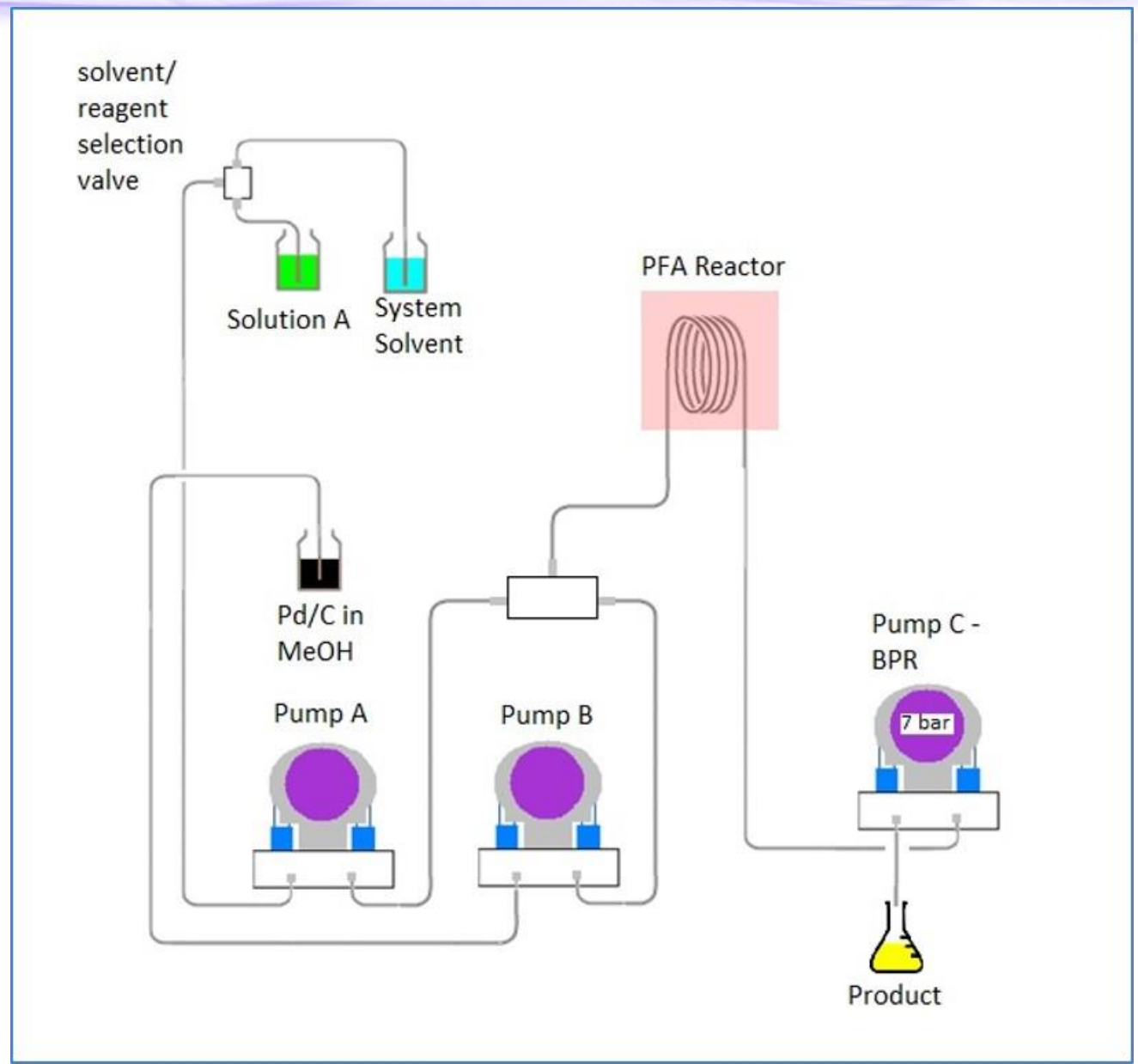


Palladium on Charcoal Slurries



1

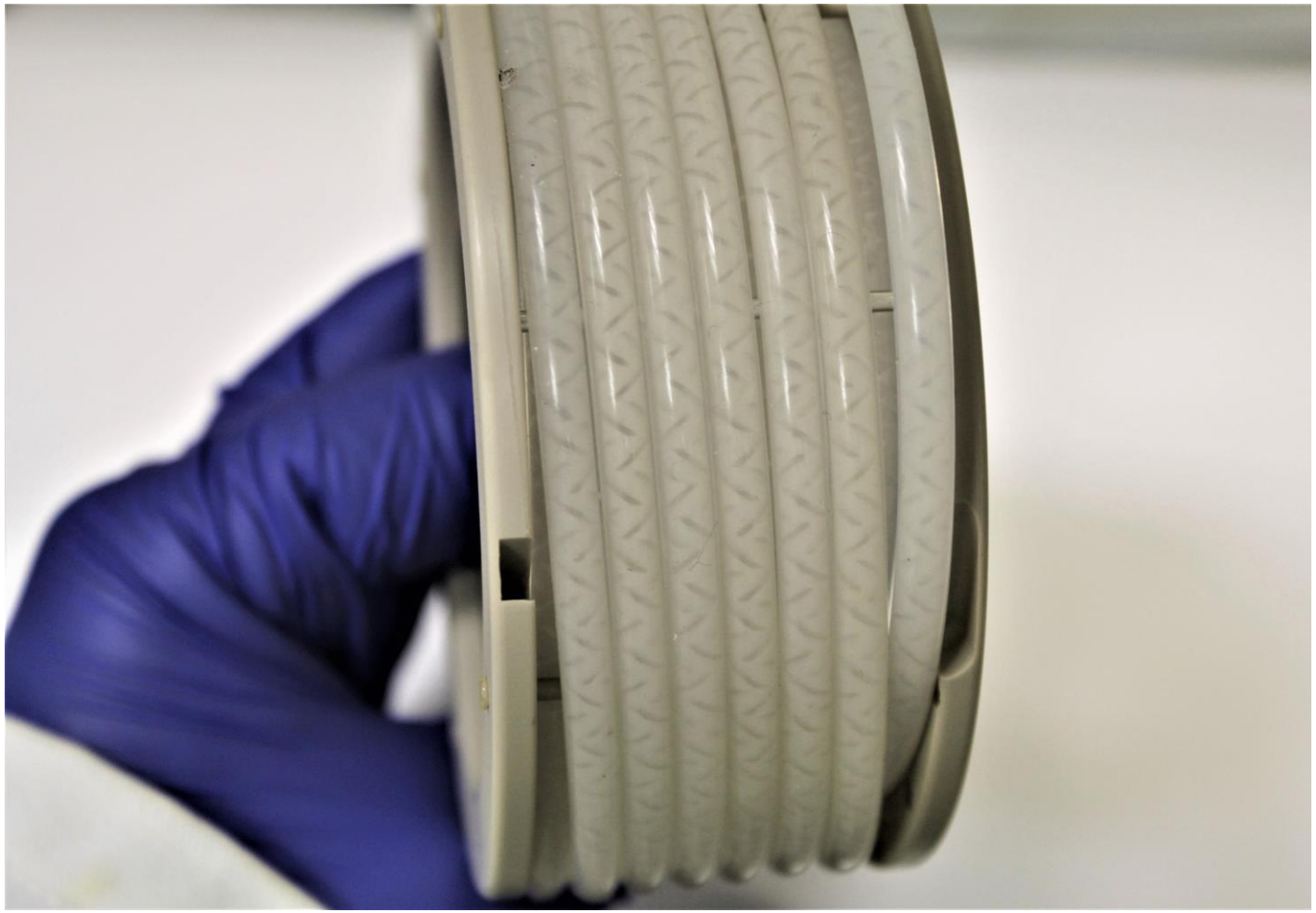
2


solvent/
reagent
selection
valve
Solution A
System
Solvent
PFA Reactor
Pd/C in
MeOH
Pump A
Pump B
Pump C -
BPR
7 bar
Product

Palladium on Charcoal Slurries

- Over **6 g/h** of an API intermediate
- Pumping slurries of 5 and 10% palladium on charcoal **under pressure** continuously
- Heterogeneously catalysed transfer hydrogenation without catalyst scale limitations enabling straightforward scale-up
- **81%** isolated yield
- Use of the V-3 pump to control back pressure
- Versatile ability to optimise catalyst conditions

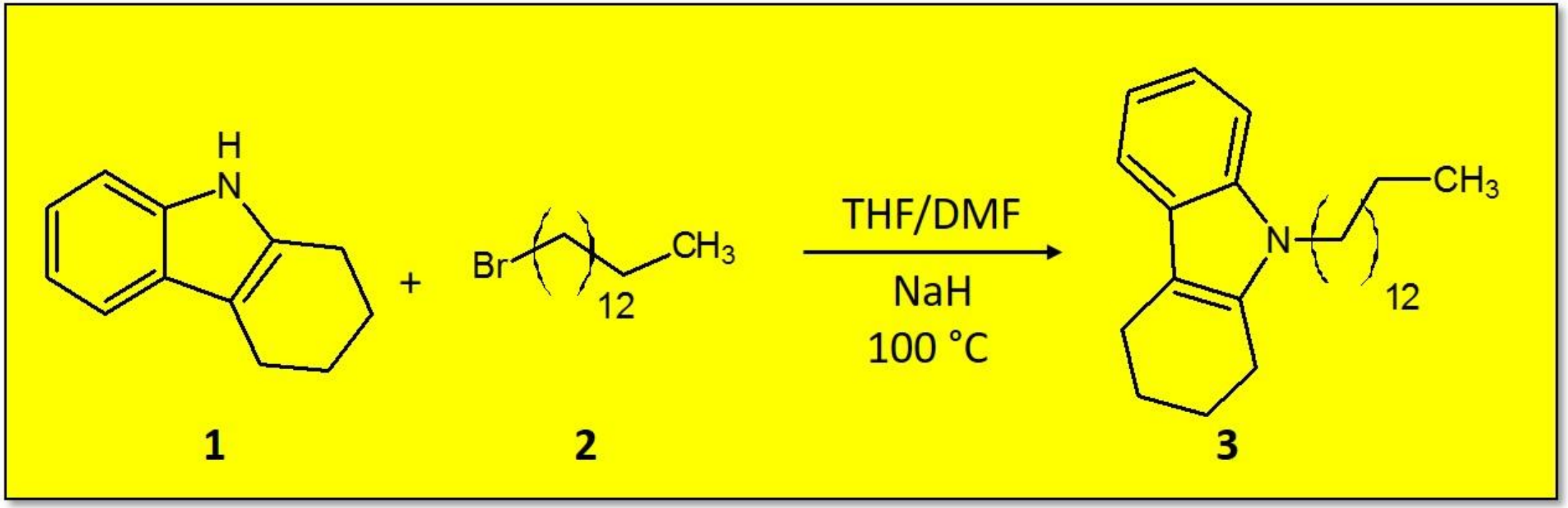
Sodium Hydride as a Slurry



Sodium Hydride as a Slurry

- Sodium hydride is one of the most versatile heterogeneous strong bases available in chemistry
- Many commercial forms of the reagent are cheaply available
- Commonly available 60% dispersion in mineral oil, a relatively stable and easily handled form
- Sodium hydride derived anions frequently lead to enhancements in yield and selectivity in a large variety of reactions

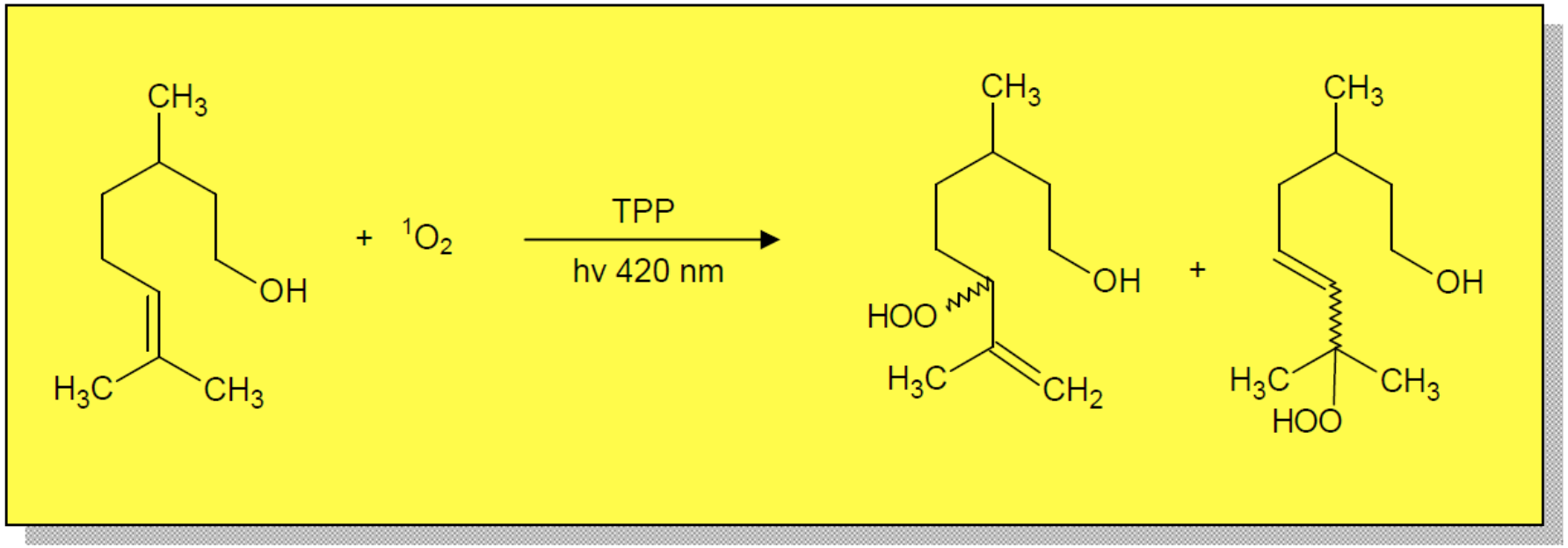
Sodium Hydride as a Slurry



Sodium Hydride as a Slurry

- Utilising sodium hydride as a slurry in THF for a laboratory scale continuous flow reaction
- Pumping the sodium hydride as a slurry and controlling gas formation by operation at a pressure of **7 bar**
- Truly continuous operation demonstrated during a **2-hour** synthesis of an alkyl carbazole heterocycle intermediate
- Fast reaction time of **4 minutes**
- 82 % isolated yield, 10.6 gh^{-1} with greater than **98%** purity

Singlet Oxygen Oxidation



- Oxygen is an ideal oxidising agent
- Clear potential dangers in its use at large scale
- Photochemical reactions can present scale-up challenges due to falling light penetration

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Features of the UV-150

- Fits both E and R-Series systems
- Multiple gram / hour scale-up
- High intensity UV light source
- User selectable UV power
- Light source wavelength filtering
- Temperature control - 40˚C to 80˚C
- Easily changed reactors
- Space saving compact design
- Interlocks ensure safe operation
- Optional spectrometer for real time monitoring of transmission spectra
- LED light sources are also available from 365 nm to 530 nm

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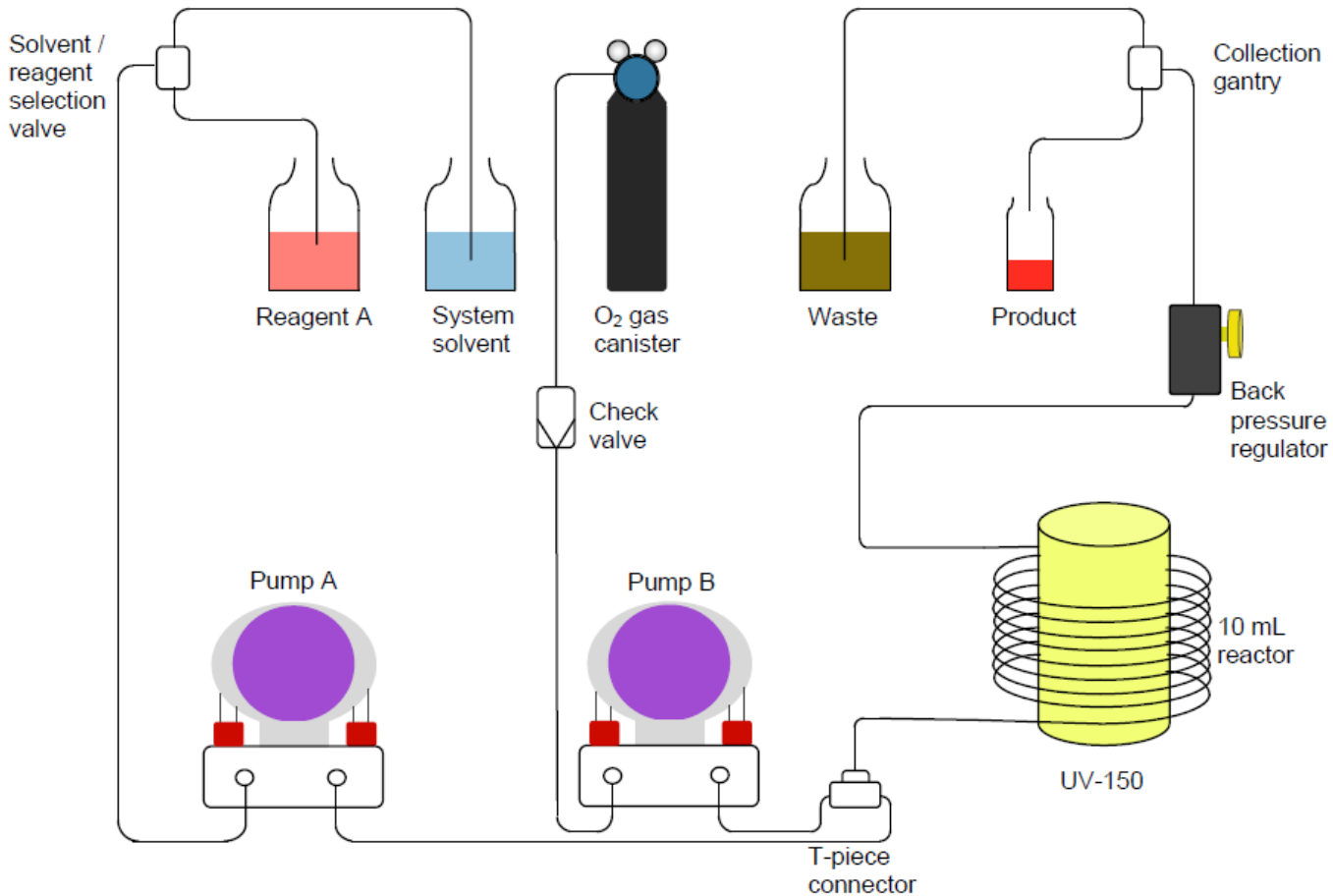

Solvent / reagent selection valve
Reagent A
System solvent
O_2 gas canister
Waste
Product
Collection gantry
Check valve
Back pressure regulator
Pump A
Pump B
10 mL reactor
UV-150
T-piece connector

Singlet Oxygen Oxidation

- Pumping of reactive gases without the need for mass flow controllers
- Variable, automated back-pressure regulation
- Ease of scale-up with the UV-150
- Variable wavelength options – target specific chromophores or activation pathways
- **15.3 g/h**

Industry and Academia

Vapourtec users include industrial **…**

- Abbot, AstraZeneca, BP, GSK, J&J, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB, Sigma Aldrich, Galderma, Novasep, Amgen, Takeda + 20 other Pharma, CROs and CMOs.

… and Academic

- Cambridge, MIT, Montreal, London (UCL), Nottingham, Cardiff Southampton, Toulouse, Bath, Paris SUD, FUNDP, Sheffield, Rennes, Milan, Kansas, CSIRO, Melbourne, Max Planck, + 10 other academic institutes.

The Vapourtec has been the system of choice for 250 peer reviewed publications to date.

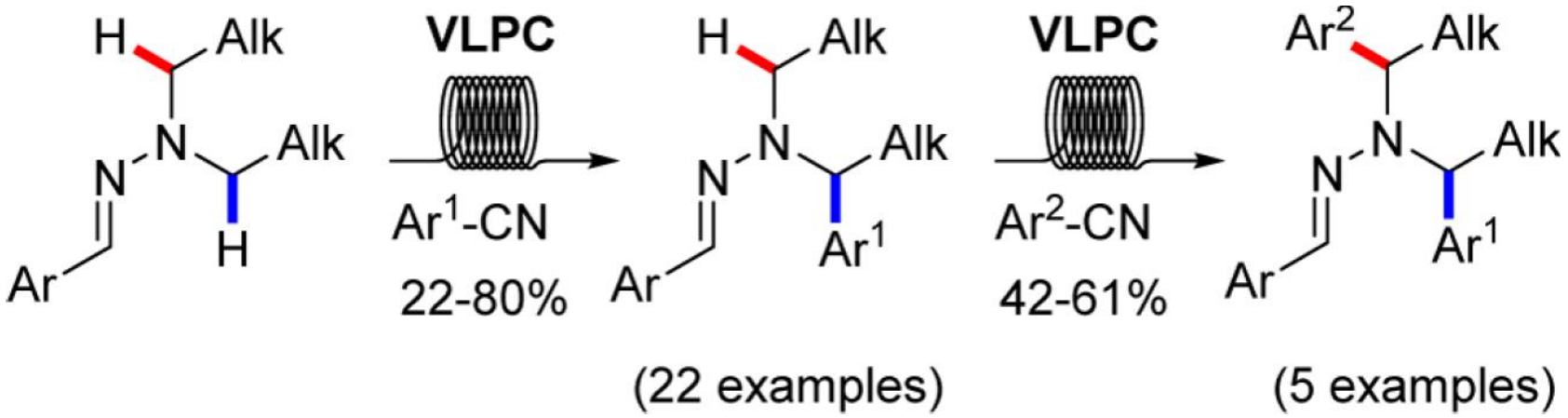
370 Vapourtec systems installed worldwide.

http://vapourtec.co.uk/publications

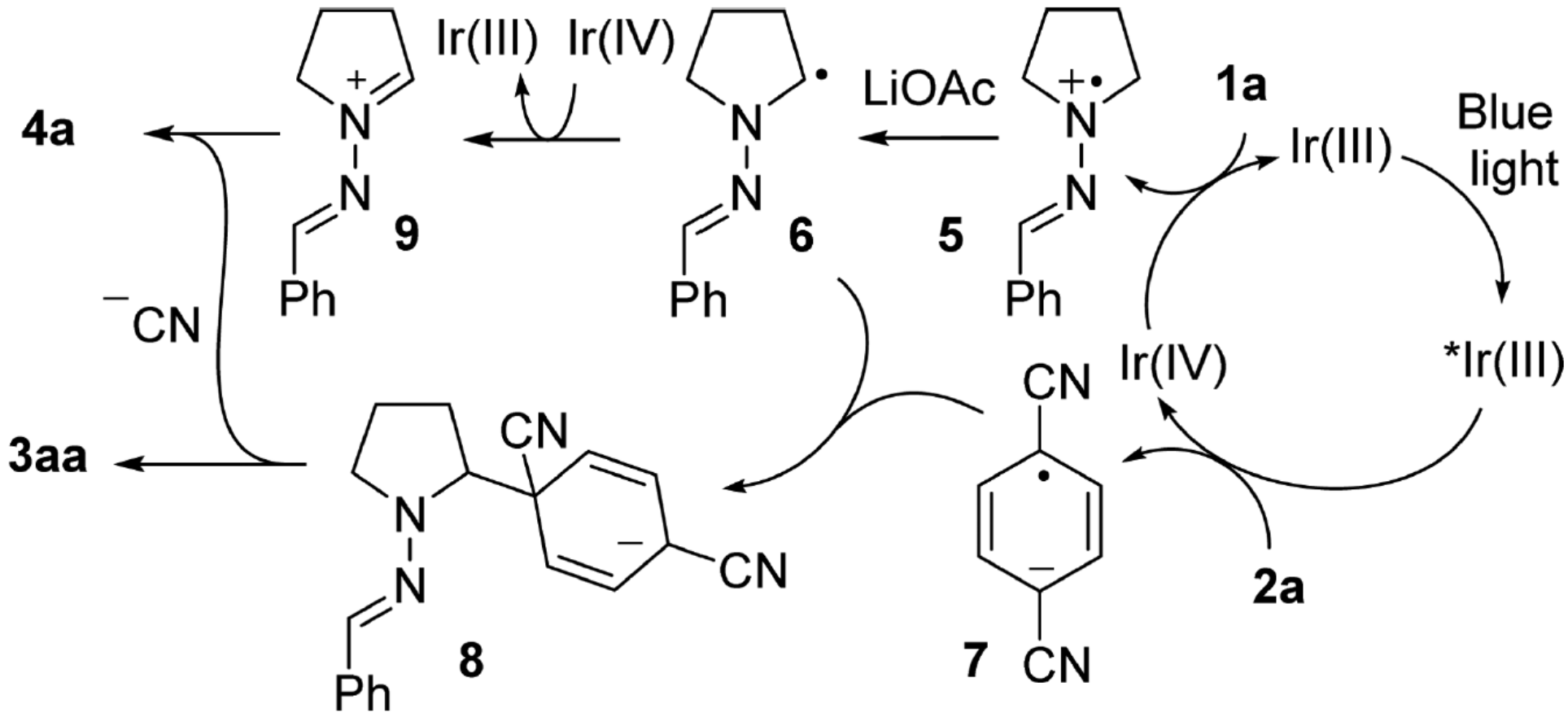
Pharmaceutical Industry

Janssen

Continuous Flow α-Arylation of N,N-Dialkylhydrazones under Visible Light Photoredox Catalysis – Andrés A. Trabanco, 2017



J. A. Vega, J. M. Alonso, G. Mendez, M. Ciordia, F. Delgado, A. A. Trabanco, *Org. Lett.*, 2017, **19**, 938-941


4a
Ir(III)
Ir(IV)
LiOAc
1a
Blue
light
Ir(III)
9
6
5
Ph
Ph
Ph
−CN
3aa
CN
CN
Ir(IV)
*Ir(III)
CN
2a
8
7
CN
Ph

Pharmaceutical Industry

- Possible to obtain conversions of 89% in batch, with high selectivity
- On scale-up, conversion fell to **54%, and 50%** selectivity

- Translate batch optimal conditions into flow

- Scale-up of optimal gave comparable results in flow, permitting **91% conversion, and 75% isolated yield**

"To our delight, the results were comparable when the reaction was scaled up to 15 mmol, and the product was isolated in 75% yield"

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Academia

Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions.

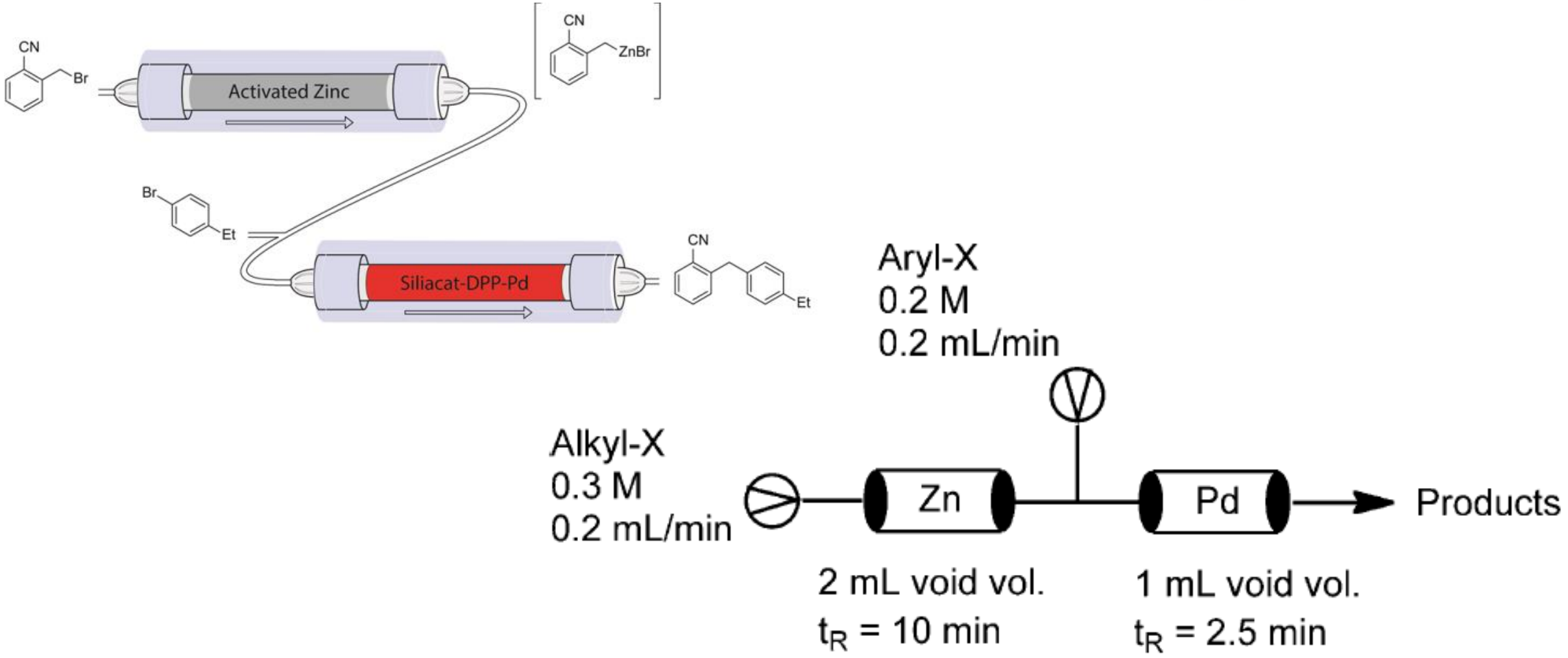
Organoboranes (Suzuki) are the most common choice in C-C bond formation and a wide range are commercially available

Organozinc (Negishi) are commercially limited in range
- superior reaction rates
- can be used when organoboranes are too unreactive
- can facilitate the coupling of sp^3 carbons

However organozinc compounds can have issues with reproducibility and handling.

If we could generate these intermediates and react them in-situ then we can increase the scope of C-C cross coupling diversity.

Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions,
Nerea Alonso, L. Zane Miller, Juan de M. Munoz, Jesus Alcazar, Tyler McQuade,
Adv. Synth. Catal.,2014, 18, 3737-3741



Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions,
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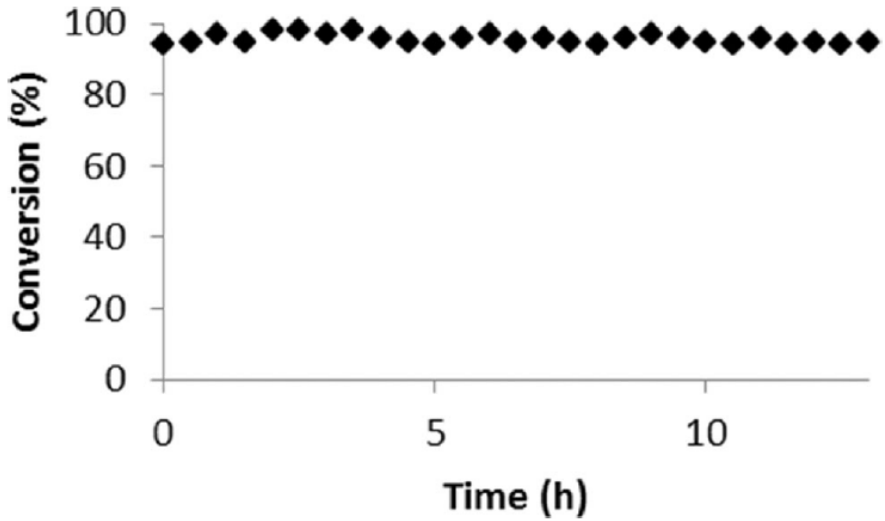
Academia



Long term stability assessment

- Column filled 12 g Zinc
- Initial trial used 5 g Zinc – 150 ml (0.5M) solution of benzyl zinc bromide (94%)
- Calculated turnover – 175
- Continuous output – 3.3 mmol h^{-1}

Approach is stable and robust enough to support larger scale chemistry

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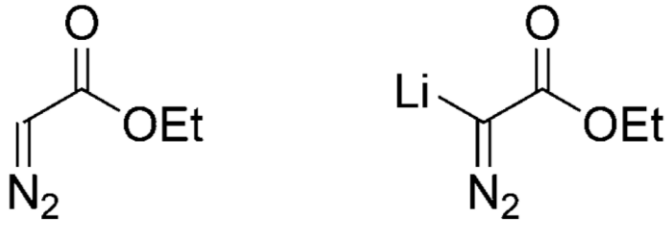
Academia

Ethyl Lithiodiazoacetate: Extremely Unstable Intermediate Handled Efficiently in Flow



Diazo compounds are highly versatile, and ethyl diazoacetate (EDA) is a common diazo reagent, that can be used as a Nucleophile under base catalysis.

Aldehydes are sufficiently electrophilc to react with EDA directly, but other carbonyl electrophiles require the use of Organometallics, such as lithium diisopropylamide (LDA), generating ethyl lithiodiazoacetate.

S. T. R. Müller, T. Hokamp, S. Ehrmann, P. Hellier,
T. Wirth, *Chem. Eur. J.,* 2016, **22**, 11940 - 11942

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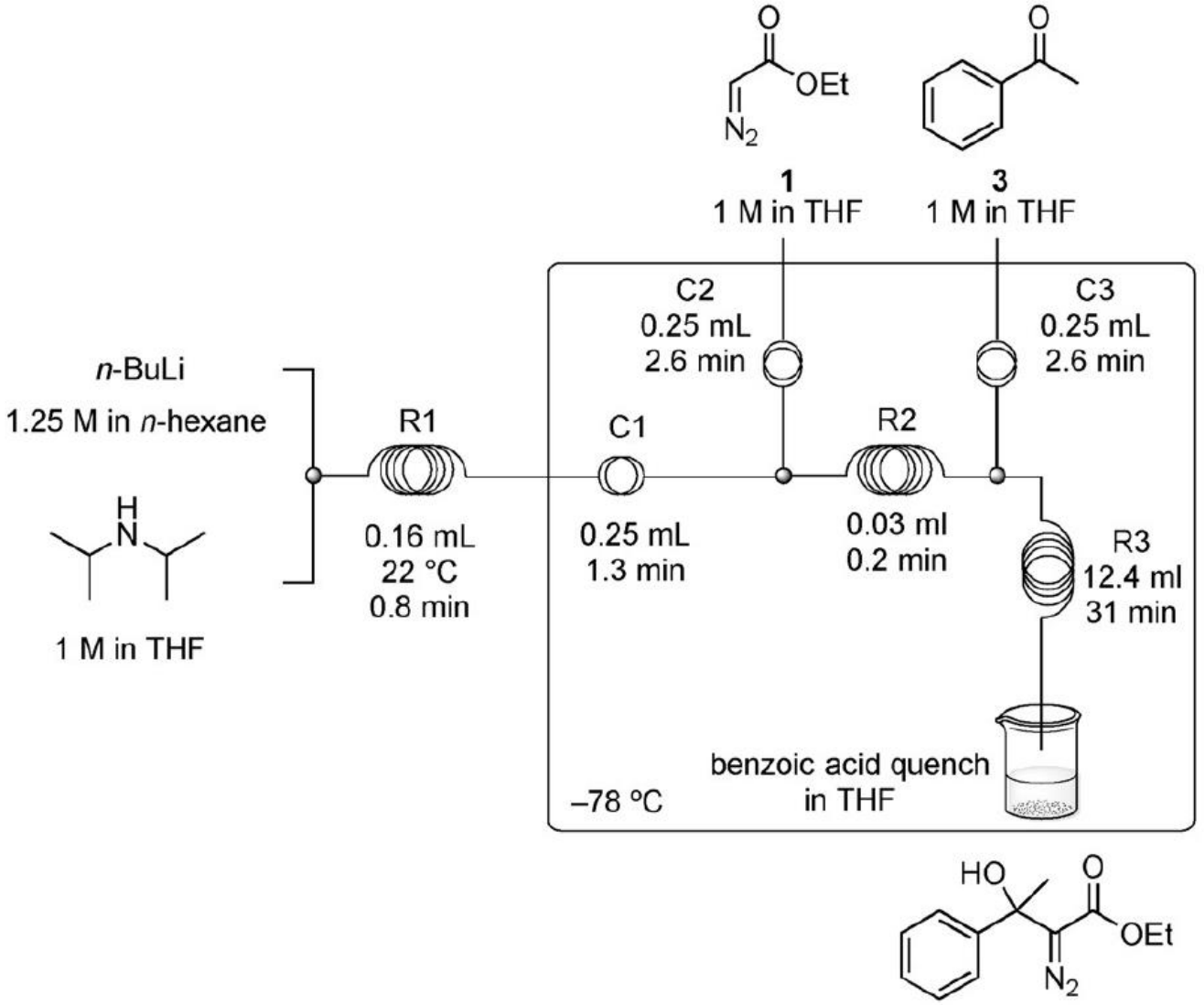

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Reactors

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Standard PFA coil
Ambient to 150 ˚C

High Temp coil
Ambient to 250 ˚C

Cooled PFA coil
Ambient to -70 ˚C

Standard Column
Ambient to 150 ˚C

Cooled column
Ambient to -40 ˚C

Gas/Liquid reactor
Ambient to 150 ˚C

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Micromixer reactor -40 °C to 150 ˚C

Photochemical reactor – 40 °C to 80 ˚C

Heated mixer reactor ambient to 150 ˚C

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New Applications of Flow Chemistry in Industry and Academia

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